REMARKS

Claims 1-44 are pending.

Claims 1-44 of the present U.S. application comprises three independent claims concerning a kind of biodegradable and thermosensitive microgel, namely, hydrogel microparticle (claim 1), the preparation technique of this kind of microgel (claim 10), and a post-fabrication encapsulation technique of drugs with employment of the properties of this microgel (claim 35).

Applicant wishes to point out that the main differences between the three patent references cited and the present application are listed as follows:

Pathak, et al. (USPN: 6,201,065) disclosed a macromer technique to prepare a kind of hydrogels, and disclosed its potential application in drug release and tissue treatment. However, the present application relates to a microgel with a definition clearly described in the specification and is different from the microsphere in Pathak, et al. patent. Applicant further disclosed the preparation method (inverse suspension polymerization) of the hydrogel particles which is not described nor disclosed in Pathak, et al. As far as the drug loading technique is concerned, Pathak, et al. merely disclosed a conventional technique of drug encapsulation during hydrogel formation; in contrast, the present application discloses and claims a unique encapsulation technique by employing the properties of the microgel.

Hubbell, et al. (USPN: 6,306,922) disclosed a technique to prepare macromers, photopolymerizible and biodegradable hydrogels, and disclosed its potential application as tissue contacting material and controlled release carriers. In contrast, the present application is about thermosensitive microgels prepared by the combination of a technique for forming a macromer with a technique of inverse suspension polymerization. Again, as the drug loading technique is concerned, Hubebell, et al. merely dislcosed a conventional technique of *in situ* encapsulation drug during hydrogel formation. In contrast, the present application discloses and claims a unique encapsulation technique by employing the thermosensitivity of the microgel of the present invention.

Scranton, et al. (USPN: 5,739,210) disclosed a copolymer comprising a reversible hydrophobic functionality by designing a donor group and an accepter group in one macromolecule. It does not describe or disclose chemically-crosslinked hydrogels. Scranton, et al. is far removed from the invention of the present application, and Applicant does not believe that there is anticipation nor obviousness issues relating to the present application.

The Examiner applied one paragraph in the "Background Of The Invention" of Scranton, et al. to contend that suspension polymerization is a routine technique.

For the Examiner's reference, the core patent technique has, after the filing of the present application, the subject matter of the application was submitted to and eventually published in the top academic journal in the field of controlled release. Enclosed herewith is a copy of the article:

Ying Zhang, Wen Zhu, Biaobing Wang, Jiandong Ding*, "A novel microgel and associated post-fabrication encapsulation technique of proteins", *J. Controlled Release*, 105, 260-268 (2005).

This paper is authored by the inventor of the present application and is focused upon Applicant's novel microgel, its preparation method, and the unique encapsulation technique based upon this gel microparticles as claimed in this application. The inventor's techniques were not regarded as obvious to the editor and referees of this authoritative journal. Therefore, it shows in some degree that the present invention is not obvious to a person of ordinary skill at the time of invention.

Rejections under 35 U.S.C. §102

Claims 1-9, 35, 40-44 are rejected under 35 U.S.C.102(b) as being unpatentable by Pathak, et al.(USPN: 6,201,065).

As amended, claim 1 and the claims dependent thereon recite a thermosensitive and biodegradable microgel with a particular structure and that the microgel is in the form of microparticles.

Pathak, et al. disclosed a multiblock macromonomer or macromer which is capable of forming biodegradable gel after polymerization. In contrast, the claims are directed to "A thermosensitive and biodegradable microgel with a chemically cross-linked network comprising at least one negative temperature-sensitive macromolecule and one biodegradable group… ", see claim 1 and a unique method loading a substance into the network of the microgel, see claim 35. Pathak, et al. disclosed a macromer and associated gel technique. But Pathak, et al did not disclose or describe the microgel technique and associated drug encapsulating technique of the present invention.

The present application is focused upon and claims a "microgel", which is significantly different from the bulk hydrogel disclosed in the Pathak, et al. patent.

Firstly, in this application microgels, namely, gel microparticles prepared from an inverse suspension polymerization technique. Whereas, Pathak, et al. did not mention this technique at all.

Secondly, as a sustained release carrier, it is not trivial to make a hydrogel in the form of a microparticle. This form of microparticle is very important for the unique drug encapsulation technique as described and claimed in claim 35. Conventionally, the pharmaceutical drug is mixed together with macromers and entrapped into the gel network during the formation of the gels by polymerization or crosslinking. The technique used in this application is by encapsulation of the drug after the preparation of a gel. This has several advantages such as the residue of un-reacted macromers is readily removed and encapsulation of proteins is easily accomplished without the use of a high temperature and any organic solvent which may destroy the conformational structure of proteins. The microparticulate form enables an effective post-encapsulation encapsulation technique and also makes it possible to produce an injectable drug-loaded gel.

Thirdly, there is the significant difference between the "microsphere" in the Pathak, et al. patent and the "microgel" in the present application. The details are as follows.

The term "microsphere" has, from the context, a specific meaning in Pathak, et al., and is different from the "microgel" of the claimed invention. The microspheres in Pathak, et al. are formed by self-assembly or aggregation of amphiphilic polymers in water. They use the term "microsphere" to describe the *mesoscopic structure* of the macroscopic hydrogel, which could be quite large with a lot of connected microspheres). See col. 12, lns. 27-43 in Pathak, et al. For convenience, these two paragraphs of Pathak, et al. are as follows:

> The microspheres are formed in one embodiment by aggregation and subsequent polymerization of portions of the macromers which are similar in charge properties such as hydrophilicity. This results in a matrix which consists of spontaneously-assembled "nodes", which may be crosslinked covalently, and may be further covalently linked to hydrophilic bridges of the macromers to form a hydrogel.
>
> When the macromer is amphiphilic and includes hydrophobic and hydrophilic domains, in an aqueous environment, at or above a certain concentration, the molecules to arrange themselves into organized structures called micelles, at the critical micellar concentration (CMC). These micelles can be of different shapes and sizes, though are generally spherical or elliptical shape. When the solution is water, the hydrophobic portions are at the center of the micelle while the hydrophilic tails orient themselves toward water. The interior core of a typical surfactant has a size

See also Fig. 12 in Pathak, et al.

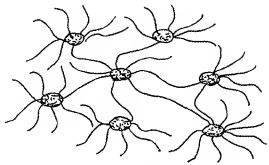

FIG. 12

FIG. **12** is a schematic illustration of nanospheres or microspheres which can be formed by aggregation and subsequent polymerization of hydrophilic macromers.

Thus, the "microspheres" in Pathak, et al. describe some "nodes" in a hydrogel instead of gel particles in an isolated form. These "nodes" are polymerized micelles, and micelles may be spherical on the order of a nanometer but deformed in at least one dimension that is much larger than a nanometer, as is well known.

Pathak, et al. col. 12, lns. 18-24, which was specifically cited in the Office Action by the examiner,

> microspheres. As used herein, the term "microspheres" includes includes particles having a uniform spherical shape or an irregular shape, and microcapsules (having a core and an outer layer of polymer) which generally have a diameter from the nanometer range up to about 5 mm. In a preferred embodiment, the microspheres are dispersed in biocompatible, biodegradable hydrogel matrices. The

Based upon these passages in Pathak, et al., a "microcapsule" essentially refers to a micelle with a structure (col. 12, lin 40-43).

Further, from the claims of Pathak, et al. this term indirectly or directly is directed to this concept. See claim 1 of Pathak, et al. as follows:

> **1**. A macromer which is capable of forming a gel, the macromer comprising a total of five or ten covalently linked polymeric blocks, wherein:
>
> a) at least one polymer block is hydrophilic and each hydrophilic polymer block individually has a water solubility of at least 1 gram/liter;
>
> b) at least two blocks are sufficiently hydrophobic to cause the macromer to aggregate to form micelles in an aqueous continuous phase;
>
> c) the macromer comprises at least one crosslinkable group;
>
> d) the macromer comprises at least one thermally sensitive region; and
>
> e) a solution of the macromer is capable of gelling or crosslinking to produce a hydrogel with a temperature dependent volume.

Thus, the gel in Pathak, et al. is formed basically in three steps: first, preparing a macromer; second, forming micelles or "microspheres" due to

aggregation or self-assembly; third, crosslinking the microsphere structures via a conventional polymerization process. It is clear from Pathak, et al. that the term "microsphere" describes the mescoscopic structure of the hydrogel and not the hydrogel itself. The hydrogel in Pathak, et al. is a macroscopic bulk gel.

In contrast, the hydrogel in the present application is a microgel formed: first, by synthesizing a macromer; second, forming droplets of a macromer aqueous solution suspended in an organic medium; third, triggering polymerization (inverse suspension polymerization) to form the claimed microgel.

In the present application, the tem microgel is not merely a description of the physical form of the underlying gel, but also the basic structure that is used (purified, isolated and applied directly to encapsulate protein drugs). In summary, the "microgel" in the claimed invention differs from the "miscosphere" of Pathak, et al. significantly. In the present application, microgel means a hydrogel microparticle which could be and have been isolated and employed to encapsulate drug after its formation, see Fig 2 of the present application. In claimed invention, the microgels were obtained by suspension polymerization, which was not described, disclosed not suggested in Pathak, et al. Therefore, claims 1- 9 cannot be regarded as anticipated by Pathak, et al.

Claims 1-7, 9, 35 and 40-44 are rejected under 35 U.S.C.102(b) as being anticipated by Hubbell, et al. (USPN: 6,306,922)

Hubbell, et al. disclosed a PEO-PPO block copolymer as one of potential candidates of the "water soluble region" of macromers (col 8 lin 2-3). However, Hubebell, et al. is not directed to a thermosensitive block copolymer. Moreover, not all of PEO-PPO block copolymers can be regarded as temperature-sensitive hydrogels, which is dependent upon block length, composition, and concentration etc. Claim 1 of this application explicitly defines a "thermosentive microgel" and a "temperature-sensitive block copolymer of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO)". It is such thermosensitivity that enables the unique post-fabrication encapsulation technique of the present application. Therefore,

claims 1-7 and 9 cannot be regarded as anticipated by the Hubbell, et al. patent, and is novel.

The Hubbell, et al. patent disclosed that the hydrogel can carry a therapeutic protein. Please *see*, col. 9, lns. 35-44 as follows:

> Controlled Drug Delivery.
> A second preferred application concerns a method of locally applying a biologically active substance to tissue surfaces of a patient. The method includes the steps of mixing a biologically active substance with an aqueous solution including a light-sensitive free-radical polymerization initiator and a macromer as described above to form a coating mixture. Tissue surfaces are coated with the coating mixture and exposed to light sufficient to polymerize the macromer. The biologically active substance can be any of

The encapsulation technique of the present invention is a post-fabrication encapsulation method. That is, after the preparation and purification of microgels, proteins were absorbed into the network of the microgel by allowing the microgel to swell in a protein solution at a low temperature below the phase transition temperature of microgels, then the protein was entrapped into the network by increasing the temperature (higher than phase transition temperature of microgels) or drying the microgels. Therefore the drug-loading technique of claim 35 and 40-44 is significantly different from that described in Hubbell, et al. patent.

Rejections under 35 U.S.C. §103

Claims 1-44 rejected under 35 U.S.C. §103(a) as being unpatentable over Pathak, et al. (USPN: 6,201,065)

Reconsideration of the rejection of claims 1-9 is requested for the reasons stated above and for claims 10-44 for the following reasons.

Claim 10 is directed to a method of preparing a thermosensitive and biodegradable microgel by inverse suspension polymerization. Pathak, et al. did not disclose, describe, or suggest using a normal suspension polymerization process,

which to a person of ordinary skill in the art, means polymerization that proceeds in an oil-in-water suspension system.

Although Pathak, et al. discloses various % wt/wt of the macromolecule in water that fall within the ranges specified in claims 16, 17-18, and 20-21, the methods of the present claimed invention are different from that of Pathak, et al. Since the process is entirely different, the coincidence in the amount of macromolecule used cannot be applied to find the claims to be obvious. Under the law, there must be something in the prior art to suggestion the use of the amounts in the process for a finding of obviousness.

In Pathak, et al., a photoinitiator was added to initiate the polymerization by visible or long wavelength ultraviolet radiation. In claims 22-31, the initiating agent is a redox agent and polymerization was initiated by increasing the temperature. In claim 33, Span, Tween or a mixture thereof was used as a stabilizer during suspension polymerization process of claim 33. The presence of the stabilizer is important for the formation of the microgel. In Pathak, et al., Tween was mentioned in Example 13 (col 22) to solubilize Taxol and was not used as a stabilizer in the process for forming the microgel.

EXAMPLE 13

Release of Tetracycline and Taxol

A 30% w/w solution of F127 trimethylene carbonate acrylate (as described in Example 3) in phosphate buffered saline, pH7.4 was prepared. 3000 ppm Darocur® (Ciba Geigy) was incorporated in the solutions as photoinitiator. Tetracycline (free base, crystalline, F.W. 444.44) was incorporated in the macromer solution by equilibration for 12 hours at 37 degrees C. Then, 200 microliters of the solution was crosslinked by UV light (10 W/cm2, full cure). In vitro release of tetracycline from the 200 microliter cured gel, after a brief rinse, was carried out in 5 mls PBS, pH 7.4, 37° C. The PBS was exchanged daily to ensure "sink" conditions. The release profile is seen FIG. 16. After an initial burst, tetracycline was released steadily for nearly a week.

Taxol was incorporated into gels by similar procedures, except that Tween™ surfactant was used to solubilize the Taxol concentrate. A similar release pattern to that seen with tetracycline was observed.

In the Pathak, et al. patent, Tween was used just to solubilize the drug Taxol, an entirely different function from that of the present invention of claim 33.

Claims 36-39 depend on claim 35, for the reasons stated above, the claimed invention being distinguishable from Pathak, et al. and cannot be regarded as obvious in view thereof. For the Examiner's reference, the encapsulation technique of the present invention was published in the authority journal in the field of controlled release ("A novel microgel and associated post-fabrication encapsulation technique of proteins", *J. Controlled Release*, 105, 260-268 (2005)). Applicant respectfully requests reconsideration and withdrawal of the §103 rejection to claims 1-44 for the above reasons.

Claims 1-32, and 33-44 are further rejected under 35 U.S.C. §103(a) as being unpatentable by Hubbell, et al. (USPN: 6,306,922).

The claims of the present application are directed to "A thermosensitive and biodegradable microgel..." (amended claim 1), which is distinguishable from the disclosures of Hubbell, et al. for the reasons stated above. Claim 10 is directed to a process by which hydrogel microparticles are formed by inverse suspension polymerization. This process is different from the suspension polymerization process disclosed in Hubbell, et al. Hubbell, et al. does not disclose formation of thermosensitive hydrogel particles because the temperature strategy in the preparation of a thermosensitive particle is somewhat critical (Ying Zhang, Wen Zhu, Jiandong Ding*, "Preparation of thermosensitive microgels via suspension polymerization using different temperature protocols", *J. Biomed. Mater. Res. Part A*, 75(2), 342-349 (2005), a copy of which is attached).

Claims 36-39 are directed to a process wherein a drug is loaded into the prepared and purified hydrogel microparticles at a low temperature and entrapped in the hydrogel by increasing the temperature over the critical phase transition of the hydrogel. Because of the uniqueness of the encapsulation technique, it is not regarded as a routine experimentation, and was approved and published in the authoritative journal, *Journal of Controlled Release*.

Claims 1-44 are further rejected under 35 U.S.C. §103(a) as being unpatentable over Hubbell, et al. (USPN: 6,306,922) in view of Pathak, et al. (USPN: 6,201,065) and in further view of Scranton, et al. (USPN: 5,739,210).

As pointed out by the Examiner, Hubbell, et al. does not use inverse suspension polymerization, and is silent on a number of reaction parameters, *e.g.,* the use of emusifiers, the temperature of the reaction during polymerization, etc.

Pathak, et al. disclose the use of Tween to solubilize the model drug Taxol. This is in contrast to the presently claimed invention wherein Tween is used as a stabilizer to form droplets prior to the process of inverse suspension polymerization.

Scranton, et al. disclose the copolymers as emulsifier in suspension polymerization. In contrast, in the present claimed invention, an inverse suspension polymerization is adopted after the formation of the macromers to prepare the microgel. The polymerization conditions are unique due to the negative thermosensitivity of the macromer.

The combination of process steps and conditions of the present claimed invention is unique. Otherwise, it would not have merited publication in the top journal in the field of controlled release. *See*, Ying Zhang, Wen Zhu, Biaobing Wang, Jiandong Ding*, *A novel microgel and associated post-fabrication encapsulation technique of proteins*, ***J. Controlled Release***, 105, 260-268 (2005).

In conclusion, the claims of the present application are mainly directed to a specific thermosensitive and biodegradable microgel (claim 1), the method of preparation thereof (claim 10), and a simple but intelligent method of loading a substance into a network of the microgel with negative temperature sensitivity (claim 35). The claimed invention is different from that of an *in situ* encapsulation technique, wherein the un-reacted macromers or impurities remain in the encapsulated hydrogel. The invention as claimed enables the encapsulation of the drug after removal of most of the remaining un-reacted macromers in hydrogel. It also avoids the use of , organic solvents and high temperature in the loading of a proteinaceous drug. The claimed microgel, the methods of preparation thereof and the post-fabrication encapsulation method are unique and are patentable.

Double Patenting Rejection

Claims 1-3, 5, 7-13 and 18-19 are provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 1-11 and 16-17 of copending application no. 10/355,161 (U.S. Publication No. 2004/0009897).

Applicant respectfully requests this be held in abeyance until one of the applications is allowed. Upon notice of allowable subject matter, applicants will address the rejection.

CONCLUSION

As amended it is believed that the claims presently presented are allowable. An early allowance is earnestly requested.

AUTHORIZATION

Applicants believe that no additional fees are necessary, however, should any such fees be due, the Commissioner is hereby authorized to charge any additional fees which may be required for this Amendment, or credit any overpayment, to Deposit Account No. 13-4500, Order No. 4614-4000.

Respectfully submitted,

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